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The Effect Of Artocarpus Altilis leaf Extracts In Reducing Blood Glucose In People With Prediabetes In Maros District, South Sulawesi Province, Indonesia Literature Review

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Abstract

As the economy improves and technology advances, changes in lifestyle also occur. These include changes in diet, decrease in physical activity, as well as increase in bad habits like smoking. It can cause pancreatic β-cell dysfunction and insulin resistance. This literature review utilizing academic databases such as PubMed, Google Scholar, and ScienceDirect included all journals recorded, classified, and analyzedin 8 years, from 2001 to 2019.Artocarpus altilis leaf extract was found to enhance the function of pancreatic β-cells and protect against free radicals. Artocarpus altilis leaf extract is recommended in reducing blood glucose.

Introduction

Nowadays, the rising economy and technological developments have brought about lifestyle changes, such as changes in diet, decreased physical activity, and adverse bad habits like smoking. The habit of consuming junk foods, which are high in carbohydrates and fat but low in fiber, ultraviolet exposure, increased air pollution both from factories and households, and uncontrolled use of pesticides in agriculture are all factors considered detrimental to one's health. Poor diet and little exercise will further cause obesity, increasing the risk of type 2 diabetes. Preventive measures are needed to maintain one's health such as eating a balanced diet, having regular exercise, eliminating bad habits, and avoiding excessive stress.**(Chong et al, 2017).**

Prediabetes is a condition where blood glucose level rises above normal but not enough to meet the criteria to diagnose it as type 2 diabetes mellitus (DM). The American Diabetes Association (2018) defines prediabetes as the condition of having fasting blood glucose level of 100–125 mg/dL and/or blood glucose level 2 hours after eating (postprandial) at the range 140–199 mg/dL. Prediabetes has risk factors including hypercholesterolemia, dyslipidemia, obesity, sedentary lifestyle, hypertension, and family history of diabetes (Mahboobi *et al.*, 2014). Prediabetes condition can sooner or later develop into type 2 DM if not prevented (Aroda, Ratner, 2008). The condition also increases the risk of people with heart disease, atherosclerosis, and other macrovascular/microvascular diseases. Prediabetes has almost twice the potential for cardiovascular risk compared to individuals without prediabetes (Ciccone *et al*., 2014).

Prediabetes is a global health problem that concerns all of us, as it is more prevalent than type 2 DM. Approximately 35.5 % of the American population was found to have prediabetes from 1999 to 2010 was over 20 years. The prevalence in the UK was recorded to be at 35.5 %, China 15.5 %, Spain 14.8 %, and Bangladesh 22.2 % (Compeán-Ortiz *et al*., 2018). Meanwhile, the prevalence of prediabetes in Indonesia in 2009 was recorded to be at 10.2 %, which drastically increased to 36.6 % in 2013 (Mihardja *et al*., 2009). According to the International Diabetes Federation (2017), Indonesia has ranked third in terms of the number of people having prediabetes aged 20–79 years old (International Diabetes Federation, 2017). Some research findings have associated prediabetes with metabolic syndromes such as obesity especially abdominal and visceral obesity, dyslipidemia, and hypertension (American Diabetes Association, 2018). The study of Kansal and Kamble (2016) showed that people suffering from prediabetes have an abnormal lipid profile compared to healthy people, a factor found to increase the risk of cardiovascular disease (Kansal, Kamble, 2016).

Type 2 DM is a chronic disease in which there is an increase in blood glucose concentration due to impaired inadequate insulin hormone secretion or impaired insulin function (insulin resistance) or a combination

of the two (International Diabetes Federation, 2017). DM is a metabolic disease known as a silent killer because the individual often does not know that he has it, and once diagnosed, it is often too late due to complications. Diabetes is also known as the mother of diseases, known to cause hyperlipidemia, hypertension, heart and blood vessel disease, stroke, kidney failure, blindness, etc. (Papatheodorou, *et al*., 2018).

In 2018, the USA has recorded 1.5 million cases of type 2 DM (age range, 18 years or older) (CDC, 2020). Globally, an estimated 422 million adults were recorded to be living with diabetes in 2014, and it will reach 21.3 million people in 2030 epidemiologically (American Diabetes Association, 2018). According to International Diabetes Federation (2017), Indonesia ranks sixth worldwide, in terms of the number of people suffering from DM, with 10.3 million reported cases (International Diabetes Federation, 2017). As per the Riset Kesehatan Dasar (Basic Health Research)data, the prevalence of DM increased from 6.9 %in 2013 to 8.5 % in 2018, which means that there were about 22.9 million of DM cases recorded from the 5-year period (Riset Kesehatan Dasar, 2018).

According to Riset Kesehatan Dasar (2018), management of type 2 DM is often done as follows: 75 % of patients taking oral antidiabetic medication (OAD), 5 % insulin injection, and 20 % the combination of both. But this treatment (using synthetic drugs) tends to have many side effects and is not safe for use in the long run as it can damage human organs; this calls for safer drugs for treatment use both in the short and long term (Taneja, Mani, Kukal, 2015). Therefore, screening for natural alternatives is very important.

Artocarpus altilis leaf has long been used empirically in traditional medicine in Indonesia and other countries; this has been seen to cure various diseases including hepatitis, heart and skin diseases, etc. and also lower blood glucose levels. These *Artocarpus altilis* leaves are found in South Sulawesi, in almost every district (Rinaldi, Kamadjaja, & Sumarta, 2018).In the past, *Artocarpus altilis* leaves were often boiled when used; its chemical contents are as follows: flavonoids, quercetin, saponins, polyphenols, hydroxylic acids, tannins, riboflavin, acetylcholine, etc. Flavonoids are antioxidant compounds that can activate oxidation reactions, which in turn have the ability to alter or reduce free radicals as well as protect and enhance the function of pancreatic β-cells in secreting the hormone insulin known to reduce blood glucose levels (Sikarwar *et al*., 2015). The objective of this study is to find references related to the therapeutic effects of *Artocarpus altilis* leaf extract in prediabetes.

METHOD

Literature review is a method used to collect journal data from research article and libraries relevant to the issue or topic raised read, recorded, and analyzed for the process of writing material. The journal search was done by identifying keywords, so as to get more literature material for review. The process of collecting data was done by filtering 100 sources of literature to 32 based on the criteria determined by the authors of each journal taken. The inclusion criteria in this literature were as follows: journals published in English, national journals published within the 8-year range from 2001 to 2019, and the journals in full text form. The exclusion criterion was that the published articles are not in their original form such as letters to the editor, abstracts only, and book reviews. The literature review was carried out on PubMed, Google Scholar, and ScienceDirect. To make the process of researching relevant journals efficient, keywords used are according to the title of the writing such as prediabetes, *Artocarpus altilis*, and DM.

RESULTS AND DISCUSSION

Prediabetes Review

Prediabetes is a glucose metabolism abnormality that results in higher blood glucose levels, but not high enough to be diagnosed as DM. The diagnostic criteria for prediabetes are shown in the Table.1.

The results of the tests that do not meet the normal criteria or have not been categorized in the criteria for DM are often classified into the prediabetes group; these includedisrupted fasting blood glucose, i.e., blood glucose levelafter 8 to 10 hours of fasting,at the range of 100–125 mg/dL and/or impaired glucose tolerance (IGT), which is postprandial plasma glucose examination after 2 hours of fasting, at the range 140–199 mg/dL. The results of the research conducted by Okosun and Lyn showed that the prevalence of prediabetes in 2010 tended to increase in America; it is estimated that 57 million Americans develop type 2 DM; this is about 5 % of cases each year.This can be slowed or prevented by reducing one's weight and increasing one's physical activity; as per research, it was found that about 70% of people with prediabetes are not aware that they have it. Prediabetes screening is important for awareness and management of the disease, as it can lessen the possibility of type 2 diabetes (Okosun, Lyn, 2015). According toRariden *et al*. (2015), there is a need for prediabetes screening in asymptomatic adults; these are people who have a body mass index greater than or equal to 25 kg/m and who have one or more of the following risk factors: sedentary lifestyle; family history of type 2 DM; women with a history of giving birth to babies ≥4 kg, a history of gestational diabetes, and polycystic ovary syndrome; hypertension or cardiovascular disease; triglyceride level >250 mg/dL or HDL level <35 mg/kg; HBA1C previously higher; and IGT or glucose fasting**(Rariden et al , 2015).**

According to Iche Andriyani Liberty and Nasrin Kodim (2014) prediabetes screening is the best way to prevent type 2 DM. Many research data confirm that prediabetes subjects develop type 2 DM later on. Patients with normal glucose tolerance show an 8 % incidence of diabetes in 5 years, whereas those with IGT show a 33 % incidence over the same time period. This shows that the effort to identify and prevent prediabetes is very important. Lifestyle changes and proper diet are some of the few factors needed to prevent or delay the development of prediabetes (Liberty & Kodim, 2014).

Development of Prediabetes into Type 2 DM

Prediabetes is one of the high risks for developing type 2 DM, which is about 5–10 % of cases per year. According to the American Diabetes Association (2018),about 70% of people with prediabetes will eventually become diabetic. Physiologically, the secretion of insulin isadjusted according to the needs of the body by β-cells in two phases. First, the secretion of insulin occurs after the stimulation of glucose from food or drinks. The secreted insulin is needed to regulate blood glucose and to keep it within normal limits. This phase is the insulin secretion that occurs immediately after the stimulation of β-cells.This phase is needed to anticipate blood glucose levels that usually rise sharply, immediately after eating. The normal phase is vital in preventing acute hyperglycemia after eating. After the end of phase 1, the task of regulating blood glucose is subsequently taken over by phase 2 secretion if the first secretion is inadequate. There is a compensatory mechanism in the form of increased insulin secretion in phase 2. The increase in insulin production is intended to meet the body's needs for blood glucose levels 2 hours after eating (postprandial) so that it remains within normal limits. Insulin deficiency directly results in adverse effects on blood glucose homeostasis as well as abnormalities in the form of cell dysfunction and insulin resistance, which are considered progressive clinically etiological factors. The pathogenesis of prediabetes has been associated with relative insulin deficiency and insulin resistance, which often result in abnormal blood glucose (Abdul-ghani, Defronzo, 2009).

Complications of Prediabetes and Type 2 DM

Patients with prediabetes have the same risk of complications with those patients having type 2 DM; these are often organ damages like the eyes, kidneys, heart, blood vessels etc. Studies show prediabetes can increase the risk of early diabetic nephropathy by 6–10 %, heart rhythm dysfunction, and erectile dysfunction. In addition, retinopathy was found to occur in about 8 % of patients with prediabetes. The decreased amount and effectiveness of insulin function or insulin resistance is found to be the cause of prediabetes. Various risk factors are identified for the emergence of prediabetes, both unmodifiable and modifiable. Various changes that occur in prediabetes patients include the risk of heart problems. Prediabetes is the same as metabolic syndrome and is a predictor of cardiometabolic risk. Chronic state of hyperglycemia, adversely affecting tissue, can cause chronic complications in various organs of the body. Patients with prediabetes have double the risk of having cardiovascular risk compared to people without prediabetes. Women with prediabetes who later develop type 2 DM have thrice the risk of contracting cardiovascular diseases than those who were able to manage the earlier condition. According to Wulandari (2014), WHO claimed that at the age of 30 years or above, an increase in fasting blood sugar by 1–2 mg per year and an increase in blood glucose 2 hours after meals by 5.6–13 mg per year can be recorded. Saltero (2017) reported that prediabetes is a risk factor for type 2 DM, but it can be prevented by modifying one's lifestyle**(Saltero et al, 2017).**

Management of Prediabetes

Broadly speaking, prediabetes management can be divided into two major parts, and these are non-pharmacological and pharmacological interventions. Prediabetes management principles are intended to prevent prediabetes from developing into type 2 DM. First, the management of prediabetes is suggested in a non-pharmacological manner, which entails modifying one's lifestyle, carrying out physical activities, and following a balanced diet; it is expected that prediabetes patients can lose weight by 5–10% every week, and this must be maintained in the long run (Indonesian Diabetes Association, 2014). Efforts made to prevent prediabetes condition from developing into type 2 DM are discussed in the next sections that follow.

A Balanced Diet

A balanced diet is a measure that illustrates the balance between the body's calorie needs and the amount of a person's calorie intake. A healthy and balanced diet in prediabetes is aimed at achieving a normal or ideal weight (Massó G*et al.*, 2009). Ideal body weight is obtained through limiting calorie intake sourced from carbohydrates and fats and increasing high-fiber foods sourced from vegetables, fruits, and vitamins. Some studies reported that a diet high in vegetables, fruit, and nuts is associated with a decreased incidence of diabetes. On the other hand, eating meat, especially processed ones, sweet foods, and foods high in preservatives is significantly related to increased incidence of DM. The UK (2010) recommends a regular diet in order to have a balanced amount of calorie intake. Eating a balanced meal regularly is very important in maintaining consistent insulin secretion (Prevalence*et al.*, 2010).

Routine and Regular Physical Exercise

Physical exercise that is carried out routinely and regularly will help the body use insulin better. Besides, physical exercise makes the body more fit and refreshed as blood circulation to organs increases and blood flow in blood vessels becomes smooth. In prediabetes, doing physical exercises must be made into a lifestyle, so it is a must that patients should be creative in choosing ways or patterns of physical exercise that are varied and fun. From various studies, there are several recommendations of physical exercise for patients with prediabetes. As per the Indian Health Service Special Diabetes Program For Indians (2011),examples of physical exercises are as follows:

a. Doing physical exercises at least 150 minutes a week with moderate intensity if you want to lose weight by 5–10% (Eltonen, 2010).
b. Doing physical exercises for at least 30 minutes at least thrice each week, with moderate intensity such as walking, swimming, jogging, aerobics, or a combination of those for 20 minutes.
c. Following a physical exercise program of moderate intensity and carrying it out regularly for 30–60 minutes, at least four times a week or at least 150 minutes a week.
d. For adults, doing physical exercises at least for 30 minutes every day, five times a week. For children, it is recommended to do 10,000 steps for an hour every day.

The Food and Drug Administration has not recommended efforts to prevent prediabetes using pharmacological therapy**(Robet, Mayer. 2006).** The current use of pharmacological therapy is individualized, taking into account the advantages and disadvantages in terms of the drugs used and the individuals who will be administered. Consider giving pharmacological drugs for prediabetes which has a high risk factor. If glucose levels during follow-up without medication have increased, although lifestyle modifications have been done, there is no other way than to carry out pharmacological intervention. Patients with prediabetes who are classified as high risk are those who have a combination of IFG and IGT, metabolic syndrome (two of three), worsenedglycemia, cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), history of gestational diabetes, and polycystic ovary syndrome (PCOS).Some of the choices for antidiabetic drugs that can be used in prediabetes are (1) metformin, (2) rootbose, (3) GLP-1 receptor agonist, and (4) thiazolindinedione. Metformin was identified as the best choice in preventing prediabetes from developing into type 2 DM (Mangan *et al*., 2018).

***Artocarpus altilis* Leaves**

Artocarpus altilis plants are tropical plants that can easily grow well in Maros District, both in the hot lowlands and in wet areas (Shamaun *et al*., 2010). There are several synonyms for *Artocarpus altilis* plants; these are *Artocarpus communis*, *Artocarpus communis* Forst, *Artocarpus altilis*, *Artocarpus incisa* L.f., and *Artocarpus altilis* (Parkinson) Fosberg (Sikarwar *et al*., 2015). The leaves of the *Artocarpus altilis* plant are widely used as an alternative medicine for diabetes, hypertension, liver cirrhosis, and skin diseases. This is because *Artocarpus altilis* leaves contain elements of flavonoid compounds, quercetin, champorol, steroids, glycosides, phenolic components, triterpenes, anthocyanins, hydrocyanic acid, acetylcholine, tannins, riboflavin, β-carotene, and vitamin C, which are found to be effective antioxidants (Sikarwar *et al*., 2015).

Pharmacological Effects of *Artocarpus altilis* Leaves on Prediabetes

Traditional medicinal plants can provide a good therapeutic effect on various metabolic diseases; often times, they are easy to find and cheaper, are easily managed, and have fewer side effects than chemical drug interventions (Nwokocha et al, 2012)**.***Artocarpus altilis* leaves contain flavonoid compounds, which are polar compounds, and because of that, they dissolve easily in polar solvents by inhibiting the α-glucosidase enzyme found in the small intestinal brush border, causing a decrease in the rate of digestion of carbohydrates into monosaccharides that can be absorbed by the small intestine, thereby reducing postprandial hyperglycemia (Raydian, Kurniawaty, Ramkita, 2017). *Artocarpus altilis* leaf extract contains carbohydrate inhibitor compounds, such as α-amylase, α-glucosidase, and sucrase enzymes, which can inhibit glucose absorption in the intestine so that blood glucose in postprandial plasma does not increase/normoglicemia (Fakhrudin *et al.*, 2015). α-Amylase, α-glucosidase, and sucrase can inhibit glucose absorption in the intestine so that there is no increase in postprandial blood glucose plasma (Fakhrudin *et al.*, 2015). Flavonoids are compounds composed of 15 carbon atoms, consisting of a propane chain (C-3) that are bound to 2 benzene rings (C-6). Flavonoids are polar compounds because they have unsubstituted hydroxyl groups. Therefore, polar solvents such as water, ethanol, methanol, ethyl acetate, or solvent mixtures can be used to extract flavonoids from various plant tissues. Flavonoids are available in nature in the form of glycosides, which are a combination of glucose and alcohol that are bound to the glycosidic bonds.

Flavonoids are found in the form of mono-, di-, or triglycosides. The hydroxyl groups in the flavonoid are bound by glucose. Flavonoids are classified into several groups which are flavonoids, isoflavonoids, and neoflavonoids. Various studies have also mentioned that flavonoid compounds act as antidiabetic agent (Leng *et al.*, 2018). Based on a research by Lukacinova *et al* (2008)**(Lukačínová et al., 2008)**, it showed that the compound flavonols and flavones are active compounds acting as antidiabetic. Epidemiological studies conducted by Marotti and Piccaglia (2002) explain that flavonoid compounds, including quercetin, have the ability to improve pancreatic function in patients with type 2 diabetes. In 2009 Jo *et al.* (2009) in his journal

proved that quercetin has the ability to inhibit the activity of α-glucosidase; the results of other studies also explain that quercetin has a significant result in inhibiting α-glucosidase compared to acarbose which so far has been used as an antidiabetic drug; meanwhile, *Artocarpus altilis* leaves are one of the natural herbal ingredients which can be used as an antihyperglycemic drug (**Jo et al, 2009),**Chaudhary & Tyagi, 2018,).

***Artocarpus altilis* leaf antioxidant**

Antioxidants are compounds that can neutralize free radicals. Human body can naturally produce antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase (GSH.Prx), or they can be obtained from plants in the form of α-tocopherol (vitamin E), β-carotene (SOT), provitamin A, ascorbic acid (vitamin C), flavonoids, phenolic compounds, etc. (Purboyo, 2009). *Artocarpus altilis* leaves contain antioxidants including phenolic and flavonoids. Phenolic is an important part of plants which is known to play a role in antioxidant activity, especially in preventing oxidative damage, which is associated with several chronic diseases like diabetes, cardiovascular disease, and cancer. Phenolic is composed of large molecules with various structures. It is characterized to have an aromatic ring that has a hydroxyl group. Phenolic compounds (ArOH) are known to reduce other compounds by transferring electrons (from -OH) to radical compounds so that cells will be more stable and their activities and functions will return to normal (Saptya, Aminah, 2013).

Flavonoids are considered hydrogen donor antioxidants that react effectively with free radicals. Besides, flavonoids are also known as antioxidants that break free chain reactions such as lipid peroxidation. Phenolic compounds, flavonoids, and tannins which are antioxidant compounds from *Artocarpus altilis* leaves function as free radical scavengers. The total content of phenolic and flavonoid compounds has an ideal chemical structure to capture free radicals; this also illustrates its ability to capture all reactive oxygen species. The antioxidant properties of flavonoids occur through several mechanisms such as the capture of free radicals, chelation with metal ions such as iron and copper, and inhibition of enzymes responsible for the formation of free radicals (Kumar, Pandey, 2007).

Quercetin is the largest flavonol group compound; quercetin and around 60–75 % glycosides of flavonoids are some of the flavonoid class active substances that can biologically protect the body from several types of degenerative diseases; this is by preventing the occurrence of fat peroxidation, oxidative damage, and cell death through several mechanisms including capturing oxygen radicals, giving protection against lipid peroxidation, and chelating metal ions. Three structural groups of quercetin, which help maintain stability and act as antioxidants when reacting with free radicals, includeo-dihydroxyl group on ring, 4-oxo group in conjugation with alkenes 2 and 3, and 3- and 5- hydroxyl groups; the function group can donate electrons to the which will increase the amount of resonance from the benzene structure of quercetin compounds (Materka, 2008).

Tannins are phenolic compounds that are soluble in water and are considered secondary metabolites. Tannin is synthesized by plants, is a compound having a molecular weight of 500–3000, and contains phenolic hydroxyl groups that enable effective cross bonds with proteins and other molecules such as polysaccharides, amino acids, fatty acids, and nucleic acids. Tannin has metal chelating properties. The process of chelating will occur according to the pattern of substitution and pH of phenolic compounds, so that hydrolyzed tannins have potential as chelating metals which have strong, stable and safe chelating power in the body (Atanassova, Bagdassarian, 2009).

Selection of *Artocarpus altilis* Leaves

The selection of *Artocarpus altilis* leaves depends on the habits done in the community such as in Bone district, Amali sub-district, and Tacippi Village; based on a survey conducted by researchers, most communities use *Artocarpus altilis* leaves to treat diabetes and hepatitis. They often use yellow *Artocarpus altilis* leaves that have not fallen off the branches yet. According to a study by Riasari (2015), which analyzed *Artocarpus altilis* leaf extract using Soxhlet apparatus, fractionation by VLC, and centrifugal chromatography HPLC analysis, it showed that dried *Artocarpus altilis* leaves (yellow not yet fallen) contain the highest amounts of flavonoids compared to green leaves, which helps in regenerating pancreatic β-cells to stabilize pancreatic function in prediabetes patients.

***Artocarpus altilis* Toxicity**

Toxicity is the damage of a substance when exposed to organisms. Toxicity can refer to the impact on all organisms such as animals, bacteria, or plants and their effects on the organism's substructure, such as cells (cytotoxicity) or body organs. Toxicity testing is an acute toxicity test assessed from LD50 that aims to find a single dose that can kill 50 % of a group of experimental animals using a single test material. Sairam and Urooj (2014) conducted a research using *Artocarpus altilis* leaves at a dose of 2000 mg/kg body weight on Wistar rats for 14 days. Then the considered parameters alanin aminotranferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase are examined. Then histological examination was done on the liver, kidneys, brain, and spleen. This study concluded nontoxicity can be obtained using 2000 mg/kgbb leaves in all parameters, which were found to be normal after examination, so it was recommended that *Artocarpus altilis* leaf extract can be used therapeutically (Sairam, Urooj, 2014). The research conducted by Juliastuti *et al*. (2017) aims to find

out the hepatoprotective effect of ethanol extract with 500 mg/kg *Artocarpus altilis* leaves in carbon tetrachloride-induced mice; the parameters examined were serum glutamic pyruvic transaminase (SGPT) and malondialdehyde, which resulted in a decrease in induced carbon tetrachloride. As for the parameters that were examined for serum glutamic pyruvic transaminase (SGPT) and malondialdehyde, it is suggested that *Artocarpus altilis*leaf ethanol extract was able to protect the liver. Empirically, people use breadfruit leaves to treat liver and kidney diseases and diabetes. One to two sheets of breadfruit leaves are boiled in 1 L of water every day (Atmaja, 2010). According to I Putu *et al*. (2015), the effective dose of breadfruit leaf extract (ethanol) in mice was determined at 100 mg/200 grbb; this dosage can be converted for suitable use in humans to avoid its possible adverse effects (Ari *et al.*, 2015).

CONCLUSION

From the description above, it can be concluded that prediabetes is a global problem that we must prevent or reduce. Prediabetes is a strong signal of type 2 DM. Highly complex risk factors such as physical inactivity, excessive food intake, smoking habits, family history of DM, and genetic factors can accelerate the progression of prediabetes to type 2 DM. *Artocarpus altilis* leaves found in Maros District can be developed for the treatment of prediabetes.

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